Supplementary Material for "Load Capacity Improvements in Nucleic Acid Based Systems Using Partially Open Feedback Control"

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1 ODE Modeling Assumptions and an ODE Model of Design II

Our modeling assumptions in derving the ODE models of Design I and Design II are as follows. We assume that there are no contributions from OFF-state switches (leaky expression) and disregard abortive transcripts (incomplete RNA products) and incomplete degradation products due to binding requirements of RNase H. Suppose the steady-state response of

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switches to RNA inputs are well approximated by Hill functions with n and m as Hill exponents. Then, using a few simplifying assumptions such as approximately first-order enzyme reactions and symmetric delays between the two switches (for details, see (*1*)), the ODE's describing the system are derived.

We next note down our ODE model for Design II. Let us refer to this model as Model II. Oscillators containing a positive-feedback loop in addition to a negative feedback are commonly found in nature both for the sino-atrial node oscillator and cell cycle oscillators, suggesting that the interlinked feedback loop architecture confers tunability for oscillators (*2*). This prediction is borne out by computational studies and synthetic implementations (*2*, *3*). To explore this possibility, in addition to the existing SW_{12} and SW_{21} that together comprised a negative feedback loop, a positive feedback loop formed by a single switch SW_{11} was introduced (*1*). This switch takes rA_1 as its regulatory activating input and produces rA_1 as its output. Using a few simplifying assumptions as above (for details, see (*1*)), the system can be represented using the following ODE's:

$$\frac{d[rA_1]}{dt} = k_p \cdot [T_{12}A_2] + k_p \cdot [T_{11}A_1] - k_d \cdot [rA_1], \tag{S.1}$$

$$\frac{d[rI_2]}{dt} = k_p \cdot [T_{21}A_1] - k_d \cdot [rI_2], \tag{S.2}$$

$$\frac{d[T_{12}A_2]}{dt} = \frac{1}{\tau}\left([T_{12}^{tot}]\frac{1}{1+\left(\frac{[rI_2]}{K_I}\right)^n} - [T_{12}A_2]\right), \tag{S.3}$$

$$\frac{d[T_{21}A_1]}{dt} = \frac{1}{\tau}\left([T_{21}^{tot}]\left(1 - \frac{1}{1+\left(\frac{[rA_1]}{K_A}\right)^m}\right) - [T_{21}A_1]\right), \tag{S.4}$$

$$\frac{d[T_{11}A_1]}{dt} = \frac{1}{\tau}\left([T_{11}^{tot}]\left(1 - \frac{1}{1+\left(\frac{[rA_1]}{K_A}\right)^m}\right) - [T_{11}A_1]\right). \tag{S.5}$$

Then this model can be expressed in the form $\dot{x} = f(x,u)$, where x is the vector of state variables — i.e., the switch states and the activator/inhibitor concentrations — given by $x = [rA_1 \;\; rI_2 \;\; T_{12}A_2 \;\; T_{21}A_1 \;\; T_{11}A_1]^T$, the control input u is given by $u = [K_I \;\; K_A]^T$, and $f(\cdot,\cdot)$ is a nonlinear function described by the equations (S.1)-(S.5). All the parameter values above have the same interpretations as for the Design I oscillator: k_p represents the first-order rate constant based on RNAP, k_d represents the first-order rate constant based on RNase H, n and m are the Hill exponents, τ is a relaxation time for the hybridization reactions, K_A is the activation threshold for the RNA activator rA_1, K_I is the inhibition threshold for the RNA inhibitor rI_2.

It is important to note that, in Design I and Design II, the switches SW_{12} and SW_{21} have identical regulatory domains. Therefore, it is reasonable to assume that the fraction of ON switch states ($[T_{21}A_1]/[T_{21}^{tot}]$ and $[T_{11}A_1]/[T_{11}^{tot}]$) follow identical trajectories given the same initial conditions. Thus, the system description reduces to the system of differential equations (1)-(4) since observing either of SW_{12} or SW_{21} provides enough information to deduce the state of the other switch. An important paramter to tune is the relative strength of positive and negative feedback, i.e., $[T_{11}^{tot}]/[T_{21}^{tot}]$: for instance, having a very strong positive feedback results in a bistable system rather than an oscillator. In conclusion, the amplified negative feedback design can be controlled as before using A_1 and A_2 as inputs, but provides an additional tunable knob for relative feedback strengths.

2 ODE Models of Design I and Design II Under DNA Tweezer Loading

Suppose the Design I of the Kim-Winfree oscillator is used to drive the DNA tweezer by coupling rI_2 to the load L (see the inset "*in vitro* or *in vivo* system" of Figure 2). Here, rI_2 binds to L to form an *active* complex L^a as per $rI_2 + L \rightarrow L^a$. The active complex L^a degrades back into L as per $L^a \rightarrow L$ if rI_2 is fully consumed and as per $L^a \rightarrow rI_2 + L$ if rI_2 is not consumed fully. Let us assume that $[L^{tot}] = [L] + [L^a]$ remains constant. We assume that the active load and the total load, i.e., $[L^a]$ and $[L^{tot}]$ are measured precisely. Then, it can be easily checked that

$$\frac{d[L^a]}{dt} = -k_r[L^a] + k_f[L][rI_2] \tag{S.6}$$

$$\frac{d[rI_2]}{dt} = k_pT_{21}A_1 - k_d[rI_2] + k_2[L^a] - k_f[L][rI_2]. \tag{S.7}$$

Thus, if Model I is coupled to the DNA tweezer then its dynamics get altered as follows: the equation (2) gets replaced by the equations (S.6) and (S.7); alternatively, if Model II is coupled to the DNA tweezer then its dynamics get altered as follows: the equation (S.2) gets replaced by the equations (S.6) and (S.7). Now, it is argued in (*4*) that $[L^a]$ can be effectively approximated by a quasi steady-state term $[\widehat{L^a}] = [L^{tot}][rI_2]/(k_r/k_f+[rI_2])$ whence it possible to disregard (S.6) completely and replace the equation (2) (or the equation (S.2), as the case may be) by the following equation:

$$\frac{d[rI_2]}{dt} = k_pT_{21}A_1 - k_r[L^{tot}]\frac{[rI_2]}{k_r/k_f + [rI_2]}. \tag{S.8}$$

Thus, the ODE model of Design I coupled to a loaded DNA tweezer is given by the system of equations (1)-(4) with (2) replaced by (S.8).

3 Extension of the Model to Account for Loading, Enzyme Deactivation, and Disturbances

A simplified system model accounting for the disturbances, enzyme deactivation, and modeling uncertanties is as follows:

$$
\begin{aligned}
\frac{d[rA_1]}{dt} &= \widetilde{k}_p \cdot [T_{12}A_2] - \widetilde{k}_d \cdot [rA_1] + \delta_1, \\
\frac{d[rI_2]}{dt} &= \widetilde{k}_p \cdot [T_{21}A_1] - \widetilde{k}_d \cdot [rI_2] - k_r[L^{tot}]\frac{[rI_2]}{\alpha + [rI_2]} - k_f[L][rI_2] + \delta_2, \\
\frac{d[T_{12}A_2]}{dt} &= \frac{1}{\widetilde{\tau}}\left([T_{12}^{tot}]\frac{1}{1+\left(\frac{[rI_2]}{K_I}\right)^n} - [T_{12}A_2]\right) + \delta_3, \\
\frac{d[T_{21}A_1]}{dt} &= \frac{1}{\widetilde{\tau}}\left([T_{21}^{tot}]\left(1 - \frac{1}{1+\left(\frac{[rA_1]}{K_A}\right)^m}\right) - [T_{21}A_1]\right) + \delta_4,
\end{aligned}
$$

where

$$
T_{12}^{tot} = T_{21}^{tot} = 100\text{nM},\ k_p = 0.05\text{sec}^{-1},\ k_d = 0.002\text{sec}^{-1},\ K_A = K_I = 500\text{nM},
$$
$$
m = n = 5, \tau = 500 \text{ sec}, \alpha = 760\text{nM},\ L^{tot} = 4000\text{nM}, \widetilde{k}_p = k_p e^{-0.00001t},
$$
$$
\widetilde{k}_d = k_d e^{-0.00001t}, \widetilde{\tau} = \tau \cdot (1 + t/10000),\quad k_r = 0.006\text{sec}^{-1},\ k_f = 7.9 \times 10^{-6}\text{nM}^{-1}\text{sec}^{-1},
$$

where the modeling uncertaintities δ_i (due to the neglected chemical reactions) are time-varying with $|\delta_i(\cdot)| < 50$nM for all i and the active load $[L]$ is also time-varying with $[L] \in [0, 4000\text{nM}]$.

It is assumed that the active load and the total load, i.e., $[L]$ and $[L^{tot}]$ are measured precisely. Likewise, it is assumed that $[T_{ij}A_j]$, $[rA_1]$ and $[rI_2]$ are measured precisely. It is further assumed that the binding constants k_p, k_d, k_r, and k_f are known precisely; their degradation with time is accounted for by using $\widetilde{k}_p$ etc. It is assumed that τ is known precisely; its increase due to the enzyme deactivation is accounted for by using $\widetilde{\tau}$. All modeling uncertainties (caused, in parts, by neglecting some chemical reactions) are lumped together into the norm-bounded time-varying signals δ_i — the bound on δ_i has been set heuristically and should be changed if it is incorrect.

4 An Overview of the $\mathcal{L}_1$ Adaptive Controller

Consider the plant

$$\dot{x}(t) = -a_m x(t) + b(u(t) + \theta x(t)) \,, \quad x(0) = x_0 \,, \tag{S.9}$$

where $x(t) \in \mathbb{R}$ is the state of the system, $u(t) \in \mathbb{R}$ is the control input, $a_m \in (0, \infty)$ defines the desired pole location, $b \in (0, \infty)$ is the known system input gain, and $\theta \in \mathbb{R}$ is a constant parametric uncertainty with the known bound $|\theta| \leq \theta_{\max}$. The control objective is to define the feedback signal $u(t)$ such that $x(t)$ tracks a given bounded piecewise continuous input $r(t) \in \mathbb{R}$ with desired performance specifications. We assume that $\|r\|_{\mathcal{L}_\infty} \leq \bar{r}$. The state x of the plant can be estimated using the following **state predictor**:

$$\dot{\hat{x}}(t) = -a_m \hat{x}(t) + b(u(t) + \hat{\theta}(t) x(t)) \,, \quad \hat{x}(0) = x_0 \,, \tag{S.10}$$

where $\hat{x}(t) \in \mathbb{R}$ is the state of the predictor. The system (S.10) replicates the plant structure (S.9), with the unknown parameter θ replaced by its estimate $\hat{\theta}(t)$. Notice that, since the state of the plant (S.9) is measured, we can initialize the state predictor with $\hat{x}(0) = x_0$. By subtracting (S.9) from (S.10), we obtain the *prediction error dynamics*

$$\dot{\tilde{x}}(t) = -a_m \tilde{x}(t) + b\tilde{\theta}(t) x(t) \,, \quad \tilde{x}(0) = 0 \,, \tag{S.11}$$

where $\tilde{x}(t) \triangleq \hat{x}(t) - x(t)$ and $\tilde{\theta}(t) \triangleq \hat{\theta}(t) - \theta$. The $\mathcal{L}_1$ adaptive controller is then obtained by synthesizing the control input u as:

$$u(s) = C(s)\hat{\eta}(s)\,, \tag{S.12}$$

where $C(s)$ is an exponentially stable, strictly proper lowpass filter, while $\hat{\eta}(s)$ is the Laplace transform of the signal

$$\hat{\eta}(t) \triangleq -\hat{\theta}(t)x(t) + k_g r(t)\,. \tag{S.13}$$

The architecture of the $\mathcal{L}_1$ adaptive controller is shown in Figure 4.

The closed–loop system (S.9), (S.10) with the $\mathcal{L}_1$ adaptive controller (S.12) does not behave similarly to the *ideal system*:

$$\dot{x}_m(t) = -a_m x_m(t) + a_m r(t), \quad x_m(0) = x_0, \tag{S.14}$$

where x_m is the state of the ideal system, due to the limited bandwidth of the control channel enforced by $C(s)$. To derive the dynamics of the reference system for the $\mathcal{L}_1$ controller, consider the case where the parameter θ is known. Then, the controller in (S.12) takes the form of the *reference controller*

$$u_{\mathrm{rf}}(s) = C(s)(k_g r(s) - \theta x_{\mathrm{rf}}(s))\,. \tag{S.15}$$

Notice that this control law aims for a partial compensation of the uncertainty $\theta x(s)$, namely, by compensating for only low–frequency content of $\theta x(s)$ within the bandwidth of the control channel. Substituting the reference controller (S.15) into the plant dynamics (S.9) leads to the $\mathcal{L}_1$ *reference system*

$$x_{\mathrm{rf}}(s) = H(s)C(s)k_g r(s) + H(s)(1 - C(s))\theta x_{\mathrm{rf}}(s) + x_{\mathrm{in}}(s)\,, \tag{S.16}$$

where $x_{\text{rf}}(t) \in \mathbb{R}^n$ is the state, and

$$H(s) \triangleq \frac{b}{s + a_m}, \quad x_{\text{in}}(s) \triangleq \frac{1}{s + a_m} x_0 .$$

Note that $x_{\text{in}}(s)$ is the Laplace transform of the ideal system's response to the initial condition. The first term in (S.16) contains the ideal system (S.14) and the filter, which corresponds to the desired behavior of the system in the absence of uncertainty. The second term depends on the uncertainty $\theta x(s)$. The transfer function $1 - C(s)$ is a highpass filter, which attenuates the low–frequency content of the uncertainty $\theta x(s)$. Thus, the $\mathcal{L}_1$ adaptive controller pursues a compensation of only the low–frequency content of the uncertainty $\theta x(s)$ within the bandwidth of the control channel.

A consequence of the lowpass filter in the control channel is that the stability of the $\mathcal{L}_1$ reference system is not guaranteed a priori, as it is for the ideal system (S.14). However, it can be verified as follows. Let $G(s) \triangleq H(s)(1 - C(s))$. Then, it can be proved that the $\mathcal{L}_1$ reference system is stable if $\|G(s)\theta\|_{\mathcal{L}1} < 1$. As a result, the inequality $\|G(s)\theta\|_{\mathcal{L}1} < 1$ must be ensured while synthesizing the $\mathcal{L}_1$ adaptive control system. It can be shown that

$$\|x_{\text{rf}} - x\|_{\mathcal{L}\infty} \leq \left\| \frac{C(s)}{1 - G(s)\theta} \right\|_{\mathcal{L}_1} \|\tilde{x}\|_{\mathcal{L}\infty} \leq \left\| \frac{C(s)}{1 - G(s)\theta} \right\|_{\mathcal{L}_1} \frac{2\theta_{\max}}{\sqrt{\Gamma}} . \tag{S.17}$$

This bound implies that the error between the states of the closed–loop system with the $\mathcal{L}_1$ adaptive controller and the $\mathcal{L}_1$ reference system, which uses the reference controller, can be uniformly bounded by a constant inversely proportional to the square root of the adaptation gain Γ. Likewise, it can be shown that

$$\|u_{\text{rf}} - u\|_{\mathcal{L}\infty} \leq \|C(s)\theta\|_{\mathcal{L}_1} \|x_{\text{rf}} - x\|_{\mathcal{L}\infty} + \left\| C(s) \frac{s + a_m}{b} \right\|_{\mathcal{L}_1} \frac{2\theta_{\max}}{\sqrt{\Gamma}} . \tag{S.18}$$

Notice that without the lowpass filter, that is, with $C(s) = 1$, the transfer function $C(s)(s + a_m)/b$ reduces to $(s + a_m)/b$, which is improper, and hence, in the absence of the filter $C(s)$, we cannot uniformly bound $|u_{\mathrm{rf}}(t) - u(t)|$. This illustrates the role of $C(s)$ toward obtaining a uniform performance bound for the control signal of the $\mathcal{L}_1$ adaptive control architecture, as compared to its nonadaptive version. We further notice that this uniform bound is inversely proportional to the square root of the adaptation gain, similar to the tracking error. Thus, both performance bounds can be systematically reduced by increasing the rate of adaptation.

5 Synthesis of the $\mathcal{L}_1$ Adaptive Controller

As is standard in $\mathcal{L}_1$ approach (see (*5*)), we perform the controller synthesis in two stages: in the first stage, we develop a feedback controller and in the second stage, we develop a method of generating the exciting input. The feedback controller is to ensure that (1) the system tracks the reference command satisfactorily, and (2) rejects the modeling uncertainties and exogenous disturbances satisfactorily. In particular, we use the $\mathcal{L}_1$ adaptive controller with switching adaptation laws described in (*6*). The notation used for the controller synthesis is summarized in Table 1, with the standard texts being (*7*) and (*8*). We say that a function $f : \mathbb{R}^n \mapsto \mathbb{R}^n$ is *continuously (smoothly) differentiable* if the derivative exists and is continuous (smooth). A function $f : \mathbb{R}^n \mapsto \mathbb{R}^m$ is said to be *Lipschitz* if there exists a constant $L > 0$ such that, for all $x_1, x_2 \in \mathbb{R}^n$, $\|f(x_1) - f(x_2)\| \leq L\|x_1 - x_2\|$. A system is said to be $\mathcal{L}_2$ stable if the energy of its output is finite for every finite energy input. We assume that a possibly vector-valued periodic signal u can be injected in the system externally as an excitation input. Now, our objective is to ensure that the system output y, comprising concentrations of possibly more than one chemical entities, tracks this signal as closely as possible, i.e., our objective is to synthesize a feedback controller which ensures that a suitable norm $\|y - u\|$ is minimized. As is standard in $\mathcal{L}_1$ approach (see (*5*)), we perform the controller synthesis in two stages: in the first stage, we develop a feedback controller and in the second stage, we develop a method of generating the exciting input. The feedback controller

Table 1: Notation

Symbol	Meaning
$(\mathbb{R}^+)$ $\mathbb{R}$	Set of all (nonnegative) real numbers
$\mathbb{R}^n$	Set of all n-dimensional real-valued vectors
$\mathbb{R}^{n\times m}$	Set of all $n \times m$ real-valued matrices
$\mathbb{Z}$	Set of all integers
$\mathcal{C}^1$	Class of continuously differentiable functions
$(\cdot)'$ or $(\cdot)^T$	Transpose of a vector or a matrix $(\cdot)$
$\langle x, y\rangle$	$= \displaystyle\int_{-\infty}^{\infty} y^T(t)x(t)dt$
$\langle x, y\rangle_\ell$	$= \displaystyle\int_{0}^{\ell} y^T(t)x(t)dt$
$\\|x\\|$	$= \sqrt{\langle x, x\rangle}$ ($\mathcal{L}_2$-norm, energy of x)
$\mathcal{L}_2$	Space of possibly vector valued signals x
	for which the energy $\\|x\\| < \infty$
	for which $\\|x\\|_\ell < \infty$ $\forall \ell \in \mathbb{R}$
$\\|z\\|_1$	$= \int_{-\infty}^{\infty} \|z(t)\| \, dt$

is to ensure that (1) the system tracks the reference command satisfactorily, and (2) rejects the modeling uncertainties and exogenous disturbances satisfactorily. For this purpose, we choose $\mathcal{L}_1$ adaptive controller, which enables fast adaptation and provides guaranteed transient performance while preserving robustness of the control system. The $\mathcal{L}_1$ adaptive control theory was originally developed for the systems with fast computing capability (*5*), which allow complicated mathematical calculations at relatively large speeds; however some of the $\mathcal{L}_1$ adaptive architectures can be suitable for implementation in chemical reactions. Namely, for the problem in this paper, we choose $\mathcal{L}_1$ adaptive controller with switching adaptation laws (*6*). This architecture has adaptation laws with simple structure and does not require large values of any of the parameters or signals. Thus the adaptive controller is designed to ensure that the system outputs $[T_{12}A_2]$, $[T_{21}A_1]$ tracks a given reference signal $r_1(t)$ and $r_2(t)$ with the performance specifications given by the *desired system*

$$\dot{x}_{\mathrm{des}_1}(t) = \frac{1}{\tau^*}(r_1(t) - x_{\mathrm{des}_1}(t)), \quad \dot{x}_{\mathrm{des}_2}(t) = \frac{1}{\tau^*}(r_2(t) - x_{\mathrm{des}_2}(t)), \tag{S.19}$$

where $x_{\mathrm{des}_1}(t)$ and $x_{\mathrm{des}_2}(t)$ are the desired values of the states $[T_{12}A_2]$, $[T_{21}A_1]$, and τ^* is a nominal value of the uncertain system parameter τ. The $\mathcal{L}_1$ adaptive controller is comprised of the state predictor, switching adaptation laws, and the control law. Let the Hill-type nonlinearity $\Omega(rI_2, K_I, n)$ be defined as $\Omega(rI_2, K_I, n) = 1/(1 + ([rI_2]/K_I)^n)$. The *state predictor* is given by

$$\begin{aligned}
\dot{\hat{x}}_1(t) &= \frac{1}{\tau^*}([T_{12}^{tot}]^*\Omega(rI_2, K_I, n) + \hat{\sigma}_1(t) - \hat{x}_1(t)), \\
\dot{\hat{x}}_2(t) &= \frac{1}{\tau^*}([T_{21}^{tot}]^*(1 - \Omega(rA_1, K_A, m)) + \hat{\sigma}_2(t) - \hat{x}_2(t)) \,,
\end{aligned}$$

where $\hat{x}_1(t)$ and $\hat{x}_2(t)$ are the predictions for $[T_{12}A_2](t)$ and $[T_{21}A_1](t)$ respectively; and $\hat{\sigma}_1(t) \in \mathbb{R}$, $\hat{\sigma}_2(t) \in \mathbb{R}$ are the adaptive estimates governed by the following *adaptation laws*:

$$\hat{\sigma}_1(t) = -\Delta_\sigma \operatorname{sgn}\left[\mathrm{dz}_{\epsilon_\sigma}\left(\tilde{x}_1(t)\right)\right], \quad \hat{\sigma}_2(t) = -\Delta_\sigma \operatorname{sgn}\left[\mathrm{dz}_{\epsilon_\sigma}\left(\tilde{x}_2(t)\right)\right] , \tag{S.20}$$

where $\tilde{x}_1(t) \triangleq \hat{x}_1(t) - [T_{12}A_2](t)$, $\tilde{x}_2(t) \triangleq \hat{x}_2(t) - [T_{21}A_1](t)$; $\mathrm{sgn}(\cdot)$ and $\mathrm{dz}(\cdot)$ stand for sign and dead–zone functions; $\epsilon_\sigma \in \mathbb{R}^+$ is the dead–zone interval; and $\Delta_\sigma \in \mathbb{R}^+$ is a design constant.

In $\mathcal{L}_1$ adaptive control theory the control signal performs compensation for the system uncertainty within the bandwidth of a lowpass filter. Notice that in our case the plant contains an input nonlinearity. This nonlinearity is invertible within admissible control input ($K_I > 0$ and $K_A > 0$). Therefore to allow compensation for the system uncertainty, we use a virtual control signals $v_1(t)$ and $v_2(t)$ and define the systems control signals using the *nonlinear inversion compensation*:

$$K_I(t) = \frac{[rI_2](t)}{\left(\frac{1}{v_1(t)} - 1\right)^{\frac{1}{n}}}, \quad K_A(t) = \frac{[rA_1](t)}{\left(\frac{1}{1-v_2(t)} - 1\right)^{\frac{1}{m}}}. \tag{S.21}$$

After substituting these control signal into the system equations, we obtain

$$\frac{d[T_{12}A_2]}{dt}(t) = \frac{1}{\tau}([T_{12}^{tot}]v_1(t) - [T_{12}A_2](t)), \quad \frac{d[T_{21}A_1]}{dt}(t) = \frac{1}{\tau}([T_{21}^{tot}]v_2(t) - [T_{21}A_1](t)) \,. \tag{S.22}$$

The system uncertainty due to variations of parameters of the above equation is compensated with the help of the following *control law*:

$$v_1(s) = C(s)(k_{g_1} r_1(s) - \hat{\sigma}_1(s)), \quad v_2(s) = C(s)(k_{g_2} r_2(s) - \hat{\sigma}_2(s)), \tag{S.23}$$

where $k_{g_1} = 1/[T_{12}^{tot}]^*$, $k_{g_2} = 1/[T_{21}^{tot}]^*$, and $C(s)$ is a stable strictly proper transfer function with unit dc gain $C(0) = 1$. This finishes the description of the $\mathcal{L}_1$ controller synthesis for Design I. The controller for Design II is obtained on similar lines.

6 Stability Proof and Performance Bounds for the $\mathcal{L}_1$ Adaptive Controller

Similar to all $\mathcal{L}_1$ adaptive control architectures from (*5*), we start the analysis by defining the $\mathcal{L}_1$ reference system, which incorporates the lowpass filter and assumes compensation of the system uncertainties only within the available bandwidth of the control channel. Then we give the performance bounds between the $\mathcal{L}_1$ reference system and the closed–loop adaptive control system for both the system output and the control input. The $\mathcal{L}_1$ reference system is given by

$$\begin{aligned}
\frac{d[T_{12}A_2]^{\mathrm{rf}}}{dt} &= \frac{1}{\tau^*}([T_{12}^{tot}]^* v_1^{\mathrm{rf}}(t) - [T_{12}A_2]^{\mathrm{rf}}(t) + \sigma_1^{\mathrm{rf}}(t)), \\
\frac{d[T_{21}A_1]^{\mathrm{rf}}}{dt} &= \frac{1}{\tau^*}([T_{21}^{tot}]^* v_2^{\mathrm{rf}}(t) - [T_{21}A_1]^{\mathrm{rf}}(t) + \sigma_2^{\mathrm{rf}}(t)), \\
v_1^{\mathrm{rf}}(s) &= C(s)(r_1(s) - \sigma_1^{\mathrm{rf}}(s)), \\
v_2^{\mathrm{rf}}(s) &= C(s)(r_2(s) - \sigma_2^{\mathrm{rf}}(s)),
\end{aligned}$$

where

$$\sigma_1^{\mathrm{rf}}(t) = \left(\frac{\tau^*}{\tau}[T_{12}^{tot}] - [T_{12}^{tot}]^*\right) v_1^{\mathrm{rf}}(t), \quad \sigma_2^{\mathrm{rf}}(t) = \left(\frac{\tau^*}{\tau}[T_{21}^{tot}] - [T_{21}^{tot}]^*\right) v_2^{\mathrm{rf}}(t).$$

Notice that the $\mathcal{L}_1$ reference system involves the system uncertainty in its definition. Therefore, it can be used only for analysis purposes. This fact also implies that the stability of the $\mathcal{L}_1$ reference system is not guaranteed apriori. Following the same steps of the proof in Section 2.4 of (*5*), the stability of the $\mathcal{L}_1$ reference system can be ensured *locally* by $\mathcal{L}_1$-norm condition similar to the one given in the Section 2.4 of (*5*). The derivations and precise equation for the $\mathcal{L}_1$-norm stability condition will be given elsewhere. If the $\mathcal{L}_1$ reference system is stable, then the performance bounds between both the system output and the control signals of the closed–loop adaptive system and the $\mathcal{L}_1$ reference system are given by

$$\|[T_{12}A_2]^{\mathrm{rf}} - [T_{12}A_2]\|_{\mathcal{L}_\infty} \leq \gamma_{x_1}, \quad \|[T_{21}A_1]^{\mathrm{rf}} - [T_{21}A_1]\|_{\mathcal{L}_\infty} \leq \gamma_{x_2}\,, \tag{S.24}$$

$$\|v_1 - v_1^{\mathrm{rf}}\|_{\mathcal{L}_\infty} \leq \gamma_{v_1}, \quad \|v_2 - v_2^{\mathrm{rf}}\|_{\mathcal{L}_\infty} \leq \gamma_{v_2}\,, \tag{S.25}$$

where γ_* are computable bounds. Due to the nature of the input nonlinearity only local results can be achieved. In other words, the system states must remain positive, which can be achieved by applying $r_1(t)$ and $r_2(t)$ within admissible set.

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